REMARKS

The Office Action dated September 17, 1999 has been received and carefully noted. The above amendments to the claims, and the following remarks, are submitted as a full and complete response thereto.

The Office Action indicates that the sequence on page 19 lacks an identifier. Page 19 has been amended to indicate that the recited sequence is SEQ ID NO:11.

Claims 6-13, 15-30 and 34-37 were objected to as being in improper dependent form. Claims 1-37 have been canceled and new claims added to the application which are in proper dependent form. In view of the cancellation of claims 1-37 and the addition of new claims to the application, applicants request that this objection be withdrawn.

Claims 29, 30, 36, and 37 were rejected under 35 USC §112, first paragraph, as lacking enablement. References will be submitted shortly which show that ghost bacterial cells are known in the art to be useful as vaccines.

Claims 1-3, 9-18, 34, 35 and 37 were rejected under 35 USC §112, second paragraph, as indefinite. Claims 1-37 have been canceled and new claims added to the application which do not contain the language found indefinite. In view of the cancellation of claims 1-37 and the addition of new claims to the application, applicants request that this rejection be withdrawn.

Claims 15-18 were rejected under 35 USC §101. As discussed above, claims 15-18 have been canceled and new claims added to the application. In view of the new claims added to the application, applicants request that this rejection be withdrawn.

Claims 1-5, 8-13, 15-19 and 22-28 were rejected under 35 USC §103(a) as unpatentable over Eliason in view of Pakula. Eliason teaches that the phage λ repressor

recognizes its operator using a recognition helix and an arm that wraps around the DNA helix. Eliason produced repressor genes encoding proteins missing all or part of the NH_2 terminal arm. Eliason does not disclose operator DNA sequences which have a different thermostability than the wild type sequences or the use of a suicide gene. Pakula discloses amino acid substitutions that increase or decrease thermal stability of Cro protein (i.e. Pakula's substitutions increase resistance of the protein to intracellular proteolysis). In contrast to the cited prior art, in the present invention the thermostability of the operator DNA sequence with regard to binding a repressor is different, not the thermostability of any specific protein. Though Pakula states that some mutations such as QL16 increase stability but adversely affect specific DNA binding, this is different from the temperature regulated gene expression of the present invention. In the present invention, the operator sequences have the higher thermostability not the repressor protein as suggested by Pakula. Eliason discloses mutated λ operator sequences (Fig. 3) and tests the temperature sensitivity of their λ repressor binding (Table 2). However, this data, shows that the operator mutations disclosed in Eliason do not have an increased thermostability of the repressor binding as compared to the wild type sequence. Table 2 shows that the binding of the wild type repressor to the operator mutation O_rv3 is less sensitive to temperature than the wild type operator sequence, but, the binding at 37°C still is 9-times (50 mM KCl) or 3-times (200 mM KCl) less than that of the wild type sequence. Thus, neither Eliason or Pakula suggest mutated operator sequences having <u>increased</u> thermostability. In view of the above comments, applicants request that this rejection be withdrawn.

Claims 19-21 and 31-34 were rejected under 35 USC §103(a) as unpatentable over Eliason in view of Pakula further in view of Vasquez. As discussed above, neither Eliason or Pakula suggest mutated operator sequences having increased thermostability. Vasquez is cited for the disclosure of a lambda operator sequence in operative linkage with a suicide gene. Vasquez does not suggest or disclose mutated operator sequences having increased thermostability and thus does not cure the deficiencies in Eliason and Pakula. In view of the fact that the cited prior art does not suggest or disclose the presently claimed invention, applicants request that this rejection be withdrawn.

Claim 6 was rejected under 35 USC §103(a) as unpatentable over Eliason, Pakula and Vasquez further in view of WO96/06164. WO96/06164 is cited for the disclosure of the use of a mutator bacterial strain. Such a strain is described on page 5 of the present application as known in the prior art. Since Vaquez and WO96/06164, do not appear to disclose the claimed selection of mutated operator DNA sequences which have an increased thermostability with regard to binding a repressor, these references do not cure the deficiencies in Eliason and Pakula as discussed above. In view of these deficiencies, applicants request that this rejection be withdrawn.

In the event this paper is not being timely filed, the applicants respectfully petition for an appropriate extension of time. Any fees for such an extension together with any additional fees may be charged to Counsel's Deposit Account 14-1060.

Respectfully submitted,
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